REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 3 and 17-20 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The examiner indicates that references AD, AF and AH have not been considered because they are not in English. Applicants clarify for the record that EP 0712931A2 (Ref. AC) is the English language counterpart of JP 8231593 (Ref. AD) and JP 8193098 (Ref. AF), and EP 0692536 (Ref. AG) is the English language counterpart of JP 327139 (Ref. AH).

Claims 3, 15, and 17-20 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the cancellation of claim 15 and the amendments to claim 3 and 17.

Claims 3 and 17-20 have been rejected under 35 U.S.C. 112, first paragraph, because the examiner states that the specification, while being enabling for the claimed method wherein the proliferated transformed tumor cells produced *ex vivo* in claim 3 or claim 17 are directly administered into a tumor of a subject to treat the tumor cells of the tumor in the subject, does not reasonably provide enablement for transplanting the proliferated transformed tumor cells at any site in the subject. The examiner states as follows:

i) Gene therapy is unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect.

ii) The parts of the specification indicated by the applicant are only speculations and the specification provides no evidence that the genomic DNA exhibited any effect as argued by the applicant.

iii) Applicant's arguments are misplaced because the usefulness of the claimed invention is not being questioned; rather the issue is whether an artisan of skill at the time of the invention would have been able to practice the claimed method, and neither the specification nor the art of record provides sufficient guidance as to how to practice the claimed invention without undue experimentation.

iv) The specification does not provide any guidance as to what vector would have been used, how an artisan would have transplanted the cells back in the subject, and at what site in the subject.

v) The specification does not provide any guidance and evidence as to whether transplanted cells *in vivo* would have produced IL-18 and whether there would have been any treatment of the tumor. This rejection is respectfully traversed.

With regard to i) to iii):

In connection with the examiner's statement that gene therapy is unpredictable, it is true that gene therapy, which was first practiced in 1990 in the United States, does not have a long established history so as to be called a technically finalized treatment method. However, in Europe and in Japan as well as in the United States, studies with gene therapy have been intensively conducted since 1990 and clinical trials on gene therapy in animals

and humans were performed prior to the date the first priority application of the present U.S. application was filed in Japan in 1996. U.S. Patents 5,399,346 and U.S. Patent 5,478,745, which were filed with the Amendment on February 21, 2002, and *The Cytokine Handbook*, ed. A.W. Thompson, Academic Press, New York, 1994, pp. 253-256, a copy of which is attached hereto, prove the situation as discussed above that gene therapy was in place in 1996. The technical contents disclosed in the above U.S. Patents and in the relevant pages of the attached *The Cytokine Handbook* (see highlighted section on pages 254-255) are the state of the art at the time the present invention was made, and therefore, would have been taken into account by the skilled artisan in practicing the claimed invention. One of skill in the art would readily understand the presently claimed invention, particularly the usefulness of the genomic DNA of the claimed invention, as disclosed in the specification from page 11, second paragraph, to page 12, first paragraph.

With regard to iv):

One of skill in the art would easily understand what vector is used in the present invention from the disclosure in the present specification from page 11, second paragraph to page 12, first paragraph and state of the art as shown, for example, in U.S. Patent 5,478,745. "Adenovirus" is taught in the specification at page 11, second paragraph to page 12, first paragraph, and it should be noted that "adenovirus" is also used as a vector in U.S. Patent 5,478,745, which shows the state of the art at the time the invention was made. Furthermore, as SEQ ID NO:1 is the amino acid

sequence of IL-18, a copy of Ju et al., *Gene Therapy* (2000) 7:1672-1679, is attached hereto as a showing that gene therapy using IL-18 and adenovirus as the vector was successful in increasing antitumor effects through efficient induction of antitumor immunity.

Furthermore, one of skill in the art would easily understand how one would transplant the cells back into the subject and at what site in the subject from the disclosure in the specification from page 11, second paragraph to page 12, first paragraph and from the state of the art as shown in, for example, U.S. Patent 5,399,346 and U.S. Patent 5,478,745. Transplanted cells are generally given back at the tumor site or under the skin. In connection with the site where the transplanted cells are given back, *The Cytokine Handbook*, pp. 253-256, a copy of which is attached hereto, shows the state of the art.

With regard to v):

With regard to the examiner's statement that "the specification does not provide any guidance and evidence whether transplanted cells *in vivo* would have produced IL-18 and whether there would have been any treatment of the tumor", applicants invite the examiner's attention to the specification from page 11, second paragraph to page 12, first paragraph, where sufficient guidance is provided for a skilled artisan.

Furthermore, the Ju et al. reference attached hereto, which was published after the present application was filed, proves the therapeutic effect of IL-18 gene therapy.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528

VERSION WITH MARKINGS TO SHOW CHANGES MADE

3(Twice-amended). A method for treating IFN-γ and/or killer cell-susceptive tumors using gene therapy, comprising:

transforming tumor cells obtained from a subject in need thereof with a composition comprising an isolated DNA molecule that comprises a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:1, where Xaa is isoleucine or threonine, and a carrier capable of introducing the isolated DNA molecule into a mammalian cell, wherein said nucleotide sequence consists of the sequence of a fragment of human genomic DNA;

proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject to treat the <u>non-transformed</u> tumor cells in the subject.

17(Twice-amended). A method for treating IFN-γ and/or killer cell-susceptive tumors using gene therapy, comprising:

transforming tumor cells obtained from a subject in need thereof with an isolated DNA molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:1, where Xaa is isoleucine or threonine, wherein said nucleotide sequence consists of the sequence of a fragment of human genomic DNA;

proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject to treat the <u>non-transformed</u> tumor cells in the subject.